

# The Women's Health Initiative

As the 21st century approaches, American women still have more questions than answers when it comes to many of their crucial health concerns, especially about their health after menopause.

But answers to many of these questions are finally in sight. They will come from the "Women's Health Initiative" (WHI), a 15-year exploration of how to prevent coronary heart disease, breast and colon cancer, and fractures from osteoporosis, a severe thinning of the bones that poses serious problems for older women.

The National Institutes of Health (NIH) launched the WHI in 1991. In October 1997, the WHI was transferred to the National Heart, Lung, and Blood Institute (NHLBI), where it is conducted as a consortium effort that is led by the NHLBI in cooperation with the National Cancer Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

The WHI is one of the largest studies of its kind ever undertaken in the United States and involves more than 40 centers nationwide and 162,000 American women, ages 50–79, about 18 percent from minority groups. Enrollment in the study began in 1993 and ended in 1998. The first results from the WHI should be released in 2005.

This fact sheet describes the WHI and offers women information about how to stay healthy as they get older. It also suggests sources to contact to learn more about the health topics discussed.

## WHI'S STUDIES

The WHI consists of three studies:

- A clinical study that tests the effects of hormone replacement therapy (HRT), diet modification, and calcium and vitamin D supplements on heart disease, osteoporosis, and colorectal cancer risk.
- An observational study that looks at the interplay between lifestyle, health, and disease risk factors.
- A community prevention study that seeks ways to get women to adopt healthful behaviors—being done with the Federal Government's Centers for Disease Control and Prevention.

Each of these studies is described more fully below.

## **Clinical Study**

The clinical study also has three parts—HRT use, dietary modification, and calcium and vitamin D supplementation. Altogether, the three parts involve about 68,000 women, who are being followed for an average of 9 years. Depending on their eligibility, women chose to enroll in one, two, or all three of the clinical study's parts.

## Hormone Replacement Therapy.

The HRT portion of the clinical study explores the therapy's long-term effect on coronary heart disease (the main form of heart disease), osteoporosis, and breast cancer risk.

#### WHY A WOMEN'S HEALTH INITIATIVE?

The WHI seeks to reduce death and disability from heart disease, osteo-porosis, and breast and colorectal cancer. Here are data about how many women are threatened by these diseases:

#### **Women Affected**

- Average age of natural menopause for U.S. women is 51
- Women over age 50 are about 14 percent of the U.S. population about 37.5 million
- About 75 percent of women have some adverse symptoms at menopause

#### **Heart Disease**

- Kills more than 370,000 women each year
- Causes about 500,000 heart attacks in women each year
- Affects about 9 million American women—including 1 in 4 women over age 65

### **Breast Cancer**

- Kills more than 46,000 women each year
- Causes about 183,000 new cases in women each year

### **Colorectal Cancer**

- Kills more than 28,000 women each year
- Causes about 51,000 new cases of colon cancer and about 16,500 of rectal cancer in women each year

# **Osteoporotic Fractures**

- About 28 million Americans suffer from osteoporosis—80 percent of those affected are older women
- Osteoporosis accounts for 1.5 million fractures every year, including more than 300,000 hip fractures

HRT has long been used for short-term relief of menopausal symptoms, such as hot flashes and flushes, sweats, and sleep disturbances. HRT is usually taken as an estrogen alone or in combination with another hormone, progestin (progesterone).

Earlier research supported by the NHLBI showed that HRT can improve some of the risk factors for heart disease after menopause, when women's risk of heart disease increases. It's commonly believed that the increased risk is linked to the drop in estrogen that occurs at menopause. But the study—called the "Postmenopausal Estrogen/ Progestin Interventions (PEPI) Trial" (see page 3)—was not long enough to answer all of the questions about HRT, such as those about breast cancer risk or prevention of heart disease itself. Those answers will come from the WHI.

HRT's possible relationship to the risk of breast cancer is one of WHI's most eagerly awaited findings. Research into this possible link has so far been inconclusive. More than 30 observational studies have yielded inconsistent results—some suggest a reduced risk, some an increased risk, and others no changed risk.

About 27,500 women are participating in the HRT study. They take hormone pills or a placebo, which looks like the drug but has no biological effect. Women with a uterus receive either estrogen plus progestin or a placebo; women who have had a hysterectomy receive either estrogen alone or a placebo. The participants are followed for 8 to 12 years and have regular checkups every 6 months.

The study uses a conjugated equine estrogen, or Premarin, which is the form most prescribed in the United States. Premarin was chosen to make WHI's findings as applicable as possible to current clinical practice. Also, most prior HRT research used conjugated equine estrogen. For the same reasons, the study uses the progestin medroxyprogesterone (MPA).

The study is able to test only one form of estrogen. However, findings from the clinical portion of WHI will be compared with information from the observational portion (see page 3). This will broaden WHI's evaluation of the benefits and risks of different forms of estrogen.

# Dietary Modification.

WHI's dietary modification portion is examining the effect of a diet low in fat but high in fruits, vegetables, and grains on the prevention of breast and colorectal cancer and heart disease.

Various observational and animal studies have suggested that a low fat diet may prevent cancer. However, some studies of individuals have either yielded mixed results or not lasted long enough to get an answer. Thus, a link between a low fat diet and cancer prevention remains unproven.

Similarly, diet has been shown to affect some of the risk factors for heart disease, such as high blood pressure and high blood cholesterol, but it has not yet been shown to reduce heart disease itself.

The WHI dietary modification study involves about 49,000 women, who are followed for 8 to 12 years. The women consume their usual eating pattern or the diet low in fat but high in fruits, vegetables, and grains. The modified diet reduces daily fat intake to 20 percent of total calories, boosts fruits and vegetables to five or more daily servings, and increases grains to six or more daily servings.

The women in the modified diet group also attend meetings with registered dietitians or nutritionists to learn about nutrition, while those following a regular eating pattern receive only standard information on nutrition. Both groups have assessments every 6 months.

If this dietary pattern is shown to reduce breast and colorectal cancer as well as heart disease, the study will lead to important recommendations for Americans' eating habits.

# Calcium and Vitamin D Supplements.

WHI's study of calcium and vitamin D examines the ability of supplements of these two nutrients to prevent fractures and reduce the risk of colorectal cancer. Past research focused mostly on bone mass, rather than fractures.

Beginning at age 50, an American woman has a 50 percent chance of developing an osteoporotic fracture during the rest of her lifetime. While effective treatments for osteoporosis are available, it is not known if using calcium and vitamin D supplements (available over the counter) will prevent fractures.

Furthermore, more than 28,000 American women die annually from colorectal cancer (see page 2). Prior studies suggest that an increased intake of calcium and vitamin D can decrease women's risk of the disease.

The calcium and vitamin D component involves about 40,000 women. It begins a year after a woman has started participation in one or both of the other portions of the trial.

Women take either 1,000 milligrams of daily calcium carbonate and 400 International Units of vitamin D daily or placebos.

All women are followed for 7 to 11 years and receive 6-month checkups.

# **Observational Study**

WHI's observational study involves about 94,000 women. The study looks for predictors and biological markers for disease. The women receive no specific intervention, but their medical history and health habits are followed for about 9 years.

The observational study should help answer such questions as the relationship between changes in body weight and the risk of death, and whether changes in blood cholesterol level predict death. Additionally, the study will look for new health factors, including genetic markers.

A key part of the observational study is its examination of new forms of HRT, in particular those that are from natural sources and those that are designer estrogens. Designer estrogens, or "selective estrogen receptor modulators" (SERMs), are substances with estrogen-like effects on some tissues and anti-estrogen effects on others.

## PEPI—HRT AND HEART DISEASE RISK FACTORS

Some crucial information already is known about how HRT affects key risk factors for heart disease. The findings come from the "Postmenopausal Estrogen/Progestin Interventions Trial," called PEPI.

PEPI was supported by the NHLBI and other units of the NIH. The study was conducted at seven clinical sites over 3 years and involved 875 women, ages 45–64.

PEPI tested four hormone regimens: estrogen alone, taken daily; estrogen taken daily and a synthetic progestin, MPA (medroxyprogesterone acetate), taken 12 days a month; estrogen and MPA taken daily; and estrogen taken daily plus micronized progesterone (a natural progesterone), taken 12 days a month.

PEPI found that each of the hormone therapies improved key heart disease risk factors. HRT use increased high density lipoprotein (HDL, the "good cholesterol"), and decreased both low density lipoprotein (LDL, the "bad cholesterol") and fibrinogen (which allows blood to clot, thus increasing the risk of heart disease and stroke). PEPI also found that HRT not only slowed the bone loss that occurs with menopause but also significantly increased bone mass.

PEPI helped to establish the first guidelines for HRT use:

- Women with a uterus should consider a combination HRT therapy that uses both estrogen and a progesterone. Those with a uterus who take estrogen alone need to have a yearly endometrial biopsy to guard against an increased risk of endometrial cancer.
- Women without a uterus should consider taking estrogen without a progesterone.

However, PEPI was not large enough and did not last long enough to answer some vital questions about HRT, including hormone therapy's long-term effects and whether its use leads to fewer cases of heart disease and stroke. Also, it could not examine whether HRT use increases the risk of breast cancer. The WHI was undertaken to answer those and other questions about HRT.

Two SERMs currently being used in the United States are Tamoxifen and Raloxifene. Both drugs have good effects: Tamoxifen keeps breast cancer from coming back; and Raloxifene increases bone density. However, the drugs appear to have some bad effects as well. For instance, Tamoxifen may increase the risk of endometrial cancer and hot flashes, and Raloxifene, which increases hot flashes, does not improve bone mass as much as estrogen.

Currently, less is known about SERMs than about estrogen itself, especially long-term risks. Also, there are no data as yet that SERMs can prevent heart disease.

As noted, HRT data from the observational study will be compared with that from the clinical study to give a more complete picture of the benefits and risks of various forms of estrogen, including SERMs and conjugated equine estrogen. For example, rates of coronary heart disease for women in the clinical study who take conjugated equine estrogen will be compared with

those for women in the observational study who use other hormone therapies, such as SERMs.

# **Community Prevention Study**

The community prevention study is testing how women can best be encouraged to adopt healthful behaviors, such as an improved eating plan, nutritional supplementation, smoking cessation, physical activity, and early detection of treatable health problems. Conducted through eight community prevention centers based at universities, the 5-year study will try to develop model programs that can be implemented nationwide.

# WHAT SHOULD WOMEN DO NOW?

Women do not have to wait until the WHI's findings are in to take action and protect their health. The NHLBI and many other health organizations have advice that women can follow now. For instance, many of the factors that increase the risk of heart disease can be modified, including smoking, high blood pressure, high blood cholesterol, overweight, and physical inactivity. Taking action is especially important for women after menopause when, as noted, their risk of heart disease increases.

Here are some steps women can take to improve their health:

- Do not smoke cigarettes. Smoking is linked to heart disease and to cancers of the lungs, breast, mouth, larynx, esophagus, urinary tract, kidney, pancreas, and cervix. It also causes 80 percent of the cases of chronic obstructive lung disease, which includes bronchitis and emphysema. And, it has been linked to a number of reproductive problems. Low-tar and low-nicotine cigarettes may somewhat reduce the risk of lung cancer, but they do not lessen the risk of heart disease or other smoking-related diseases. There is no safe way to smoke.
- Prevent or control high blood pressure. High blood pressure, or hypertension, makes the heart work harder and can lead to heart disease, stroke, and other conditions. High blood pressure also is the number one risk factor for congestive heart failure, a serious condition in which the heart cannot pump enough blood to supply the body's needs. Congestive heart failure is increasing among older Americans, especially women. One reason may be that older women are not adequately controlling their high blood pressure.

Optimal blood pressure is less than 120/80 mm Hg. To prevent or control high blood pressure, women should lose excess weight, become physically active, choose foods lower in salt and sodium, limit alcohol intake, and, for those with high blood

# TALKING WITH YOUR DOCTOR

Women need to be involved in their health care. Ask questions and express your concerns. Here are some sample questions:

- Should I take hormones? Why? Do I have other options?
- How could hormone therapy improve my heart disease risk factor profile? Will it prevent me from developing heart disease?
- At what age should I begin HRT?
- Should I begin HRT even though I went through menopause many years ago?
- What is the best regimen for me? Why?
- How long should I stay on the therapy?
- If breast cancer has occurred in my family, should I consider HRT?
- If I have had breast cancer, should I consider HRT?
- What followup tests will I need? How often will I need to have each test?

Your risk profiles for heart disease, osteoporosis, and colorectal cancer may change over time. So remember to review your health status with your doctor regularly.

#### SOME ADDED QUESTIONS ABOUT THE WHI

Will WHI give answers about the health of minority women?

The WHI has more data on the health of minority women than any other study. About 30,000 minority women are enrolled in the WHI. Of the 40 centers participating in the clinical study, 10 recruited mostly minority women. Women from all minorities have been encouraged to participate in WHI, which includes African Americans, Hispanics, Asian Americans and Pacific Islanders, and Native Americans.

WHI's findings should give answers for minorities overall and the major subgroups. Also, the WHI researchers will analyze data for efficacy and safety by minority. Is the WHI studying Alzheimer's disease?

The WHI includes a study of participants' cognitive function. Part of the clinical and observational studies, it is evaluating the effect of hormones on memory.

The WHI also has another study of the effect of hormones on Alzheimer's disease. The study is known as the "WHI Memory Study" and is conducted by the Bowman Gray School of Medicine. It involves women in the WHI's HRT study who are age 65 and older.

Where is the WHI being done?

The WHI is a huge undertaking. As noted, the clinical and observational studies are being done at centers in 40 communities. These are in 23 States plus Washington, DC. The coordinating center for the clinical and observational studies is the Fred Hutchinson Cancer Research Center in Seattle, WA. It coordinates the study's data collection, management, and analysis.

The community prevention study is being done through eight university community prevention centers. For a list of the participating centers, write to the NHLBI Information at the address given on page 8.

pressure, take medication if prescribed. (See separate items for more about weight, physical activity, a healthy diet, and alcohol.)

 Prevent or control high blood cholesterol. The body makes all the cholesterol it needs. Extra saturated fat and cholesterol in the diet cause fatty buildup inside blood vessels.

All women should keep their cholesterol levels down to lessen the chance of developing heart disease. For those who already have heart disease, it is particularly important to treat elevated blood cholesterol to prevent a future heart attack.

Between ages 45 and 55, women's cholesterol levels begin to rise higher than men's. After age 55, the gap widens. The higher a woman's blood cholesterol level, the higher her risk of heart disease.

To lower high blood cholesterol, adopt a healthy eating plan, become physically active, and lose excess weight. (See separate items for more on each of these.) Additionally, some women may need to take cholesterol-lowering medication. The degree to which cholesterol should be lowered depends on whether or not a woman already has heart disease.

 Eat a healthy diet rich in fruits, vegetables, and low fat dairy products, and low in saturated fat, total fat, and cholesterol.

Healthy women should get less than 10 percent of their day's total calories from saturated fat and less than 30 percent from total fat, and have less than 300 milligrams of dietary cholesterol a day. Women with high blood cholesterol should follow the same plan but be sure to have only 8-10 percent of the day's calories from saturated fat. Women with heart disease should follow the same total fat amount as others but have less than 7 percent of the day's total calories from saturated fat and less than 200 milligrams of

dietary cholesterol a day. Anyone with a health risk or illness should talk with their doctor about their eating plan.

Women also should be sure they get 1,000–1,500 milligrams of calcium each day. After menopause, women should get 1,500 milligrams of calcium each day. Lowfat or fat free dairy products and foods fortified with calcium are the best sources of dietary calcium. To reach the goal, women may need to supplement their diet with calcium carbonate tablets.

They also may need to take a supplement of vitamin D. The Recommended Dietary Intake of vitamin D is up to 400 International Units each day. This is especially important for women who do not get enough sunlight or who do not have vitamin-D fortified foods.

More information on healthy eating is available from the NHLBI and the NCI. See page 8 for how to contact them.

#### WHY DIFFERENT TYPES OF STUDIES?

Medical researchers conduct many types of studies. Different types yield different information. Together, these studies help scientists understand health and disease, and how to educate people so they can lead healthier lives.

WHI includes three types of studies—clinical, observational, and community prevention. Each type is discussed below:

Clinical studies control and compare specific medical interventions, such as the use of HRT. Women on an intervention are compared with those not receiving the treatment. In clinical studies involving a drug, neither the women nor the researchers typically know who is receiving an active drug and who a placebo. These studies help reveal a causal link between a treatment and a specific medical outcome, such as fewer heart attacks. They are considered to be the "gold standard" among types of studies because they yield the most reliable information.

Observational studies follow women's medical and lifestyle practices but do not intervene. Such studies can turn up possible relationships between behaviors and health or illness. For instance, researchers can track women who do and do not take HRT. The results may show that the HRT users have less heart disease. But the results cannot conclude that HRT reduces the risk of heart disease. Other behaviors may have played a part. Women who choose to use HRT may be healthier than those who don't. Or, women who choose to use HRT may also be more likely to be under a doctor's care and so receive treatment to prevent heart disease.

Community prevention studies explore methods to encourage people to adopt healthier behaviors.

Those who drink alcohol should do so in moderation. Some studies have reported that moderate drinkers have less heart disease than those who don't drink or who drink too much. However, drinking adds calories and provides no nutrients. Also, too much alcohol is a risk factor for high blood pressure and can cause heart problems. And binge drinking can contribute to stroke.

For women, moderate drinking is defined as no more than one drink a day. One drink equals 12 ounces of regular beer, or 5 ounces of wine, or 1.5 ounces of 80-proof liquor.

■ Use a moderate amount of salt and sodium. Salt and sodium affect blood pressure. Most Americans should try to get no more than 2,400 milligrams of sodium daily. That equals about 6 grams of table salt (sodium chloride)—about 1 teaspoon. This includes all salt and sodium consumed, including whatever is in processed foods, used in cooking, or added at the table. Some women are particularly sensitive to sodium and may need to consume less.

Maintain a healthy weight. Overweight/obesity is the second most preventable cause of death in the United States—smoking is number one. Women should follow a healthy eating plan and be physically active. To maintain a healthy weight, energy expended must equal energy taken in as calories.

For those who are overweight, it is important not to gain more. Remember that weight loss involves a change of lifestyle—that will last a lifetime. Anyone trying to lose weight should not seek a quick fix. Try to lose ½ to 1 pound a week. Doctors and nutritionists can help those trying to lose weight.

■ Be physically active. Physical activity helps to control weight and reduce stress. It is one of the best ways to control heart disease, for those who already have the condition. And physical activity builds bone and improves agility and balance, which are important as women get older.

Becoming physically active does not take a lot of time. Women should try to get at least 30 minutes of moderate-level activity on most, and preferably all, days of the week. Examples of a moderate-level activity are brisk walking or gardening. If necessary, women can break up the 30 minutes into shorter periods of at least 10 minutes each.

Most women can start a physical activity program right away. But women who have heart disease should check with their physician first. This is especially important for those who are over age 55, inactive, or have diabetes or another medical problem.

■ With menopause, women face the decision of whether or not to take HRT. The box on page 3 offers some guidelines on HRT, based on the latest available research.

The decision of whether or not to use HRT depends on a woman's medical profile, including her family medical history and what risk factors or conditions she has. Women should discuss the question with their doctor. The most common reason for using HRT is to treat the symptoms of menopause, such as hot flashes. This treatment usually is needed only for a few months or years, although women with osteoporosis may need many years of treatment with estrogen or with other drugs, such as Alendronate.

Women can help prevent bone loss by being physically active and getting enough calcium. The box on page 4 suggests some questions to ask about using HRT.

HRT is not a first-line option to help women prevent heart disease. The first clinical study to look at HRT's effect on heart attacks recently reported that no decrease occurred. The "Heart and Estrogen/ Progestin Replacement Study" (HERS) involved 2,763 postmenopausal women with heart disease. After about 4 years, there was no reduced chance of heart attack from HRT use. Furthermore, during the first year of HRT use, women's risk of a heart attack increased. However, that risk decreased again after the second year. The results were unexpected and underscore the need for more clinical studies such as WHI in order to see if HRT prevents heart disease.

Also, as noted, women can reduce the risk of heart disease by reducing their risk factors for it. And a low dose of aspirin may help some women prevent a heart attack, especially if they're over age 50. Aspirin also may decrease the chance of stroke. Additionally, beta blockers, a medication used for high blood pressure and chest

#### OTHER TRIALS ON HRT AND HEART DISEASE

The WHI mostly involves women who do not have heart disease. The NHLBI also supports trials to better understand how HRT use affects heart disease in women who already have the condition.

Here are three ongoing trials that involve older women with heart disease. All of the trials use a test called a "coronary angiography," or "coronary arteriography." The test is used to assess blockages caused by atherosclerosis, a process that leads to the build up of fatty substances in blood yessels.

 "Women's Angiographic Vitamin and Estrogen" (WAVE) Trial.

This trial involves 400–450 women. It is looking at how the use of postmenopausal HRT and/or antioxidant vitamins C and E affect the progression of coronary artery disease.

"Women's Estrogen/Progestin and Lipid Lowering Hormone Atherosclerosis Regression Trial" (WELL-HART).

This trial has 226 postmenopausal women with coronary artery disease and moderately elevated low density lipoprotein (LDL) cholesterol. Coronary artery disease is a form of heart disease in which the main, or coronary, artery of the heart has reduced blood flow due to atherosclerosis. LDL carries most of the cholesterol in the blood and can lead to buildup and blockage in arteries. The trial is comparing the effects of estrogen, estrogen plus progestin (Premarin), and a placebo on the progression of the coronary artery disease.

"Estrogen Replacement and Atherosclerosis" (ERA) Trial.

This trial also is comparing the effects of estrogen, estrogen plus progestin, and a placebo on the progression of coronary artery disease in 309 postmenopausal women.

pain, have been shown to reduce the risk of a repeat heart attack. Women should talk with their doctor about taking a low dose aspirin or beta blockers.

# A FINAL WORD

As women age, their risk of heart disease, colorectal cancer, and osteoporosis increases, and it becomes even more important to follow a healthy lifestyle. Each year, ever more American women enter the post-50 age group. For them, the WHI promises answers for some of their most pressing health questions.

For more information about how to follow a healthy lifestyle, contact the sources listed in the box on page 8. Many of these offer free fact sheets, brochures, and other information.

#### **FIND OUT MORE**

Women can start now to reduce their risk of heart disease, osteoporosis, and colorectal cancer. Here are some sources of information to put you on the path to better health:

#### **About Heart Disease**

■ Visit the NHLBI Web Site

The NHLBI Web Site has much information about heart disease and related topics. Some information is available in Spanish. The Web site address is http://www.nhlbi.nih.gov/.

■ Contact the NHLBI Information Center

The NHLBI Information Center has fact sheets, brochures, and other information about heart disease and related topics. Write to the center at P.O. Box 30105, Bethesda, MD 20824-0105, or phone (301) 592-8573. Some information is available in Spanish.

■ Call the NHLBI Information Line at 1-800-575-WELL

This information line gives recorded messages about the prevention and control of high blood pressure and high blood cholesterol—two key heart disease risk factors. Callers also can leave their name and address to receive such free information as heart-healthy recipes and a booklet to help older women control their high blood pressure. The information line's messages are available in English and Spanish.

 Order The Heathy Heart Handbook for Women

This publication is a workbook to help women reduce their risk of heart disease. Newly updated, it includes a sample walking program, a quit-smoking guide, and heart-healthy recipes. A copy costs \$5.50, which includes postage and handling within the United States. Contact the NHLBI Information Center at the address given above.

#### **About Osteoporosis**

 Visit the National Institute of Arthritis and Musculoskeletal and Skin Diseases Web Site

The Institute has much information on its Web site, which is at http://www.nih.gov/niams/.

 Contact the NIH Osteoporosis and Related Bone Diseases-National Resource Center

This center provides resources and information about metabolic bone diseases, such as osteoporosis and Paget's disease.

The center's address is 1232 22nd Street, NW, Washington, DC 20037-1292. Or phone 1-800-624-BONE or 202-223-0344; Fax 202-293-2356; TTY is 202-466-4315.

#### **About Colorectal Cancer**

Contact the Cancer Information Service (CIS)

This nationwide network of 19 regional offices is supported by the National Cancer Institute (NCI) and gives accurate up-to-date information about cancer.

Contact CIS at 1-800-4-CANCER (1-800-422-6237). TTY is available at 1-800-332-8615. CIS operates Monday through Friday, 9:00 a.m. to 4:30 p.m. local time

■ Visit the NCI Web Site

NCI has much information on its Web site at http://www.nci.nih.gov/.

### About the WHI

■ Visit the WHI Web Site

For general information and updates about the WHI, check check the study's Web site at http://www.nhlbi.nih.gov/whi/.

About the NIH Office of Research on Women's Health (ORWHI)

For general information on women's health research at NIH visit: http://www4.od.nih.gov/orwh/overview.html

